Original Article

Risk factors for acute ischemic stroke following intravenous thrombolysis: a 2-center retrospective cohort study

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Background: The risk factors associated with in-hospital poor neurological function after intravenous thrombolysis in patients with acute ischemic stroke (AIS) is of major public health interest. The aim of the present study was to screen for risk factors associated with in-hospital poor neurological function after intravenous thrombolysis in patients with acute AIS.

Methods: This was a population-based cohort study. A total of 878 AIS patients who were admitted to advanced stroke centers of 2 Grade A tertiary hospitals in China between January 2018 and January 2020, and who had undergone intravenous thrombolysis therapy, were included in the present study. Baseline and treatment data of participant were collected. Poor neurological function was defined as National Institutes of Health Stroke Scale (NIHSS) score ≥16 on day 7 after onset, indicating stroke severity. Univariable and multivariable analyses were used to screen out factors associated with the endpoint.

Results: After multivariable analysis, risk factors, such as age [odds ratio (OR): 1.099, 95% confidence interval (95% CI): 1.052–1.194, P<0.001], NIHSS2 (NIHSS score immediately after thrombolysis, OR: 1.286, 95% CI: 1.201–1.377, P<0.001), total cholesterol (CHOL; OR: 1.614, 95% CI: 1.036–2.514, p<0.05), urea nitrogen (UREA; OR: 1.205, 95% CI: 1.045–1.390, P<0.05), computed tomography 24 h after thrombolysis (CT2; OR: 6.153, 95% CI: 2.696–14.045, P<0.001), and lower limb deep venous thrombosis (LDVT; OR: 4.398, 95% CI: 1.560–12.398, P<0.05) were found to be associated with poor neurological function. Lipid regulation (OR: 0.065, 95% CI: 0.02–0.215, P<0.001) and high-density lipoprotein cholesterol (HDL-C; OR: 0.038, 95% CI: 0.007–0.202, P<0.001), were found to be protective factors to avoid poor neurological function.

Conclusions: Age, NIHSS2, CHOL, UREA, CT2, and LDVT were found to be risk factors of poor neurological function after thrombolysis for AIS. Lipid regulation and HDL-C were found to be protective factors of poor neurological function.

Keywords: Poor neurological function; risk factors; acute ischemic stroke (AIS); intravenous thrombolysis

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Introduction

Concerns about stroke have focused on the associations between reperfusion therapy and neurological function after treatment. Acute ischemic stroke (AIS) is caused by a clot or embolus blocking an artery in the brain; this accounts for 69.6–70.8% of the total stroke population in China (1,2). Stroke is a leading cause of permanent disability worldwide (3). After stroke onset, survivors are at increased risk of poor outcomes and are often unable to independently perform their daily activities (4,5). These adverse

consequences cause considerable expenses in health care and losses in the labor force and economy (6). Reperfusion therapy is the main treatment option for AIS, and can significantly improve patient outcomes (7,8). Intravenous thrombolysis in the early stage of acute cerebral infarction is a safe and reliable option (7,9-11). However, due to differences in age, stroke severity before thrombolysis, and past medical history, some patients can have complications, such as symptomatic intracranial hemorrhage, vasogenic edema, and even unfavorable neurological outcomes after thrombolysis (7,9-11). Therefore, factors associated with poor neurological function after intravenous thrombolysis for AIS patients need to be accurately determined to adjust the subsequent therapeutic regimens and clinical management. Some studies have found that National Institutes of Health Stroke Scale (NIHSS) score, computed tomography (CT), transcranial Doppler ultrasound, and blood lipids levels, are associated with stroke neurological function (12-22). The review of Shakti Shrestha has discussed main factors that can affect the outcomes of treatment in ischemic stroke (23).

The primary objectives of the study were to screen the risk factors for poor neurological function in AIS patients after intravenous thrombolysis and to guide the clinical strategies. In our study, univariate analysis and multivariate analysis were used to screen out the risk factors for poor prognosis in patients with acute ischemic stroke after intravenous thrombolysis, laying a foundation for later individualized prediction and intervention. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3652/rc).

Methods

Study design

We used a 2-center cohort design in the present study. All of the patients had undergone intravenous thrombolysis between January 2018 and January 2020. Data of general information and intervention information of the patients were collected between February 2020 and April 2020. All the data using in the study came from official sites-Bigdata Observatory Platform for Stroke of China and were collected originally just for administrative purposes.

Setting

AIS patients from the advanced stroke centers of the Second Hospital of Hebei Medical University and Baoding No.1 Central Hospital were recruited between January 2018 and January 2020. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Baoding No. 1 Central Hospital (No. 2021[012]) and had been put on record in the Second Hospital of Hebei Medical University. Individual consent for this retrospective analysis was waived. Intravenous thrombolysis strategies were classified into 2 types according to the current intravenous thrombolysis guidelines for stroke (7), as well as the actual thrombolytic regimens used at the stroke centers. Type 1 was based on recombinant tissue plasminogen activator (rt-PA), and type 2 used domestic urokinase (UK). Therapeutic regimens were developed by experienced and professionally trained attending physicians at the stroke centers. We assessed neurological function according to NIHSS score in medical records before, immediately after, and 24 h after intravenous thrombolysis; neurological function according to NIHSS score was also assessed on day 7 after stroke onset.

Participants

A total of 1,009 AIS patients who underwent intravenous thrombolysis at the 2 stroke centers from January 1, 2018 to January 1, 2020 were included in the present study. After excluding ineligible participants, 878 AIS patients were included in the present study.

The inclusion criteria were as follows: (I) met the current AIS diagnostic and treatment guidelines and intravenous thrombolytic therapy criteria (7); (II) underwent intravenous thrombolysis at the stroke center within 6 h after the onset of AIS; and (III) had complete clinical, demographic, and laboratory data. The exclusion criteria were as follows: (I) wake-up stroke; (II) received bridging therapy after intravenous thrombolysis; and (III) lost to follow up.

Based on the published literature (24,25), an NIHSS score ≥16 indicated that the neurological deficit after thrombolysis was extremely severe, and it was classified as 1. An NIHSS score <16 indicated that there was no severe neurological deficit after thrombolysis, and it was classified as 0.

Variables

General data included age, sex, body mass index (BMI), history of smoking, and history of alcohol consumption. Past

medical history included hypertension, diabetes, coronary heart disease, arrhythmia, hyperlipemia, and stroke history. Systolic pressure, diastolic pressure, and emergency random peripheral blood glucose (GLU) were detected.

Data detected by routine blood test, coagulation function test, and biochemical test from the emergency laboratories in the 2 stroke centers were collected. The following reports were collected: brain CT examined before thrombolysis (CT1) and re-examined 24 h after thrombolysis (CT2); emergency electrocardiogram (ECG) examined before thrombolysis; head magnetic resonance imaging (MRI); carotid duplex ultrasound, ultrasound cardiogram (UCG), lower extremity artery ultrasound, and lower extremity venous color Doppler ultrasound examined after thrombolysis. Before thrombolysis, the NIHSS score, modified Rankin Scale before the stroke (mRS) score, and swallowing function were evaluated by experienced and professionally trained physicians. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification was adopted (26).

The time from onset to thrombolysis (OTT) and the time from door to needle (DNT) were recorded. Thrombolytic complications were observed after thrombolysis. Thrombolysis complications included bleeding in the skin and mucous membranes or gums, nasal cavity, digestive tract, urinary system, or other sites; reperfusion injury; allergies; and edema of the tongue or throat during thrombolysis.

Laboratory tests after thrombolysis included fasting venous blood glucose, glycosylated hemoglobin, homocysteine, thyroid-stimulating hormone, serum free thyroxine, serum free triiodothyronine, antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), and blood lipids.

The training regimen of rehabilitation within 72 h after thrombolysis was collected. Antiplatelet and anticoagulation therapies performed within 48 h and lipid-lowering therapy was also collected. Refer to data measurement.

These variables were independent variables (*Table 1*). In the statistical analyses, the factor considered potential confounders was OTT time. Factors considered potential effect modifier were OTT time and thrombolytics type.

When NIHSS score on day 7 after onset was ≥16, the dependent variable Y was denoted as 1.

Data measurement

In dichotomous variables, we define higher or more severe level as 1.

Two types of Thrombolytic drugs were used in the study, therefore, we defined the type of thrombolytic preparations as 2 classification variable. For example: the variable of thrombolytic type was defined as: 1: rt-PA; 2: UK.

The variable of TOAST was defined as a multivariate variable according to its own classification: 1: large artery atherosclerosis; 2: cardioembolism; 3: small artery atherosclerosis; 4: stroke of other determined etiology; 5: stroke of undetermined etiology.

The variable of "infarction position" was defined as a multivariate variable according to the brain magnetic resonance angiography (MRA) detected within 48 h of thrombolysis: 1: anterior circulation cerebral infarction (ACCI); 2: posterior circulation cerebral infarction (PCCI); 3: ACCI and PCCI: both anterior and posterior circulations had infarcts.

The variable of mRS score referred to the mRS score before the stroke onset, and was defined as a rank variable according to its own classification: 0: completely asymptomatic; 1: despite the presence of symptoms, there is no apparent disability and patients are able to perform all their usual duties and activities; 2: mildly handicapped; unable to perform all activities previously performed, but able to carry out personal affairs without help; 3: moderately handicapped; needs some assistance, but does not need assistance to walk; 4: severely disabled; unable to walk without assistance, and unable to care for their own physical needs; 5: severely disabled; bedridden, incontinent, requiring constant nursing and care; 6: death.

Water swallow test was used to evaluate swallow function in the study. The variable of swallow function was defined as a rank variable according to its result: 1: can successfully swallow water 1 time; 2: divide more than 2 times, can swallow without choking cough; 3: can swallow it all at once, but coughs; 4: swallow more than 2 times, but cough; 5: cough frequently and cannot swallow it all.

The variable of "ECG" was defined as a 2 classification variable according to its report detected in the emergency room: 0: the report suggested "normal ECG"; 1: manifestations, including atrial fibrillation, atrial flutter, various of ventricular or supraventricular arrhythmia, and ST-T changes.

The variable of "CT 1" was defined as a 2 classification variable according to its report detected 24 h after thrombolysis: 0: normal or no early infarction, 1: has early infarction.

The variable of "CT 2" was defined as a 2 classification

Table 1 Descriptive statistics and univariable analysis of all variables in the complete set

Variables	n[a]	Poor neurological status (NIHSS score ≥16), n=810	Good neurological status (NIHSS score <16), n=68	OR	P
General information					
Sex, n (%)				1.065	0.815
Male	605	46 (7.6)	559 (92.4)		
Female	273	22 (8.1)	251 (91.9)		
Age (years)	878	67.72±11.31	60.99±11.49	1.056	<0.001*
BMI (kg/m^2)	878	24.67±2.96	24.85±3.10	0.981	0.638
Smoking, n (%)	413	394 (95.4)	19 (4.6)	0.409	0.001*
Drinking, n (%)	309	295 (95.5)	14 (4.5)	0.453	0.009*
Hypertension, n (%)	549	45 (8.2)	504 (91.8)	1.188	0.518
Diabetes, n (%)	177	16 (9.0)	161 (91.0)	1.240	0.472
Coronary heart disease, n (%)	167	17 (10.2)	150 (89.8)	1.467	0.193*
Arrhythmia, n (%)	112	19 (17.0)	93 (83.0)	2.989	<0.001*
Hyperlipemia, n (%)	78	5 (6.4)	73 (93.6)	0.801	0.645
Stroke history, n (%)	208	20 (9.6)	188 (90.4)	1.379	0.250
Information about therapy					
OTT (min)	878	100.84±72.18	122.9±80.46	0.996	0.030*
DNT (min)	878	173.65±103.50	134.86±93.32	1.004	0.001*
Systolic pressure (mmHg)	878	154.66±27.43	149.81±21.05	1.010	0.076*
Diastolic pressure (mmHg)	878	83.91±13.40	86.39±14.03	0.987	0.16*
NIHSS 1 (score at admission)	878	17.71±6.79	6.64±5.14	1.282	<0.001*
NIHSS2 (score immediately after thrombolysis)	878	19.56±8.97	5.46±5.04	1.304	<0.001*
NIHSS 3 (score 24 h after thrombolysis)	878	19.81±9.38	5.28±5.09	1.302	<0.001*
Thrombolytics type, n (%)				1.270	0.425
1 (rt-PA)		52 (7.4)	652 (92.6)		
2 (UK)		16 (9.2)	158 (90.8)		
mRS (before stroke onset), n (%)				2.390	<0.001*
0	261	8 (3.1)	253 (96.9)		
1	140	1 (0.7)	139 (99.3)		
2	110	2 (1.8)	108 (98.2)		
3	125	2 (1.6)	123 (98.4)		
4	178	23 (12.9)	155 (87.1)		
5	64	32 (0.5)	32 (0.5)		
6	0	0	0		

Table 1 (*continued*)

Table 1 (*continued*)

Variables	n[a]	Poor neurological status (NIHSS score ≥16), n=810	Good neurological status (NIHSS score <16), n=68	OR	P
Swallowing function (before thrombolysis), n (%)				2.308	<0.001*
1	671	17 (2.5)	654 (97.5)		
2	63	1 (1.6)	62 (98.4)		
3	12	3 (25)	9 (75)		
4	27	3 (11.1)	24 (88.9)		
5	105	44 (41.9)	61 (58.1)		
TOAST, n (%)				0.492	<0.001*
1 (LAA)	482	47 (9.8)	435 (90.2)		
2 (CE)	81	19 (23.5)	62 (76.5)		
3 (SAA)	290	2 (0.7)	288 (99.3)		
4 (SOE)	14	0	14 (100)		
5 (SUE)	11	0	11 (100)		
Infarction position, n (%)				0.764	0.178*
1	594	54 (9.1)	540 (90.9)		
2	173	5 (2.9)	168 (97.1)		
3	111	9 (8.1)	102 (91.9)		
Thrombolytic complications, n (%)	158	28 (17.7)	130 (82.3)	3.662	<0.001*
Controlled pressure, n (%)	454	38 (8.4)	416 (91.6)	1.200	0.474
Controlled glucose, n (%)	155	15 (9.7)	140 (90.3)	1.354	0.323
Antithrombotic therapy, n (%)				2.652	0.001*
1	748	48(6.4)	700 (93.6)		
2	130	20 (15.4)	110 (84.6)		
Lipid regulation, n (%)	848	49 (5.8)	799 (94.2)	0.036	<0.001*
Rehabilitation, n (%)				0.774	0.026*
1	512	48 (9.4)	464 (90.6)		
2	126	11 (8.7)	115 (91.3)		
3	63	1 (1.6)	62 (98.4)		
4	123	4 (3.3)	119 (96.7)		
5	54	4 (7.4)	50 (92.6)		
Accessory examination					
CT1, n (%)				7.178	<0.001*
0	849	58 (6.8)	791 (93.2)		
1	29	10 (34.5)	19 (65.5)		

Table 1 (*continued*)

Table 1 (*continued*)

Variables	n[a]	Poor neurological status (NIHSS score ≥16), n=810	Good neurological status (NIHSS score <16), n=68	OR	P
ECG, n (%)				11.402	0.001*
0	210	2 (1.0)	208 (99.0)		
1	668	66 (9.9)	602 (90.1)		
CT2				16.474	<0.001*
0	727	20 (2.8)	707 (97.2)		
1	151	48 (31.8)	103 (68.2)		
MR, n (%)				11.645	<0.001*
0	672	18 (2.7)	654 (97.3)		
1	206	50 (24.3)	156 (75.7)		
Carotid duplex ultrasound, n (%)				0.844	0.647
0	745	59 (7.9)	686 (92.1)		
1	133	9 (6.8)	124 (93.2)		
UCG, n (%)				1.693	0.118*
0	775	56 (7.2)	719 (92.8)		
1	103	12 (11.7)	91 (88.3)		
Lower extremity artery ultrasound, n (%)				0.385	0.019*
0	685	61 (8.9)	624 (91.1)		
1	193	7 (3.6)	186 (96.4)		
LDVT, n (%)				4.209	<0.001*
0	817	54 (6.6)	763 (93.4)		
1	61	14 (23.0)	47 (77.0)		
ANA, n (%)				0.303	0.243
0	839	67 (8.0)	772 (92.0)		
1	39	1 (2.6)	38 (97.4)		
ANCA, n (%)				1.723	0.478
0	862	66 (7.7)	796 (92.3)		
1	16	2 (12.5)	14 (87.5)		
WBC (10^9/L)	878	9.23±3.24	7.95±2.72	1.148	<0.001*
RBC (10^{12}/L)	878	4.52±0.53	4.64±0.49	0.612	0.049*
HGB (g/L)	878	139.21±16.70	144.75±15.12	0.978	0.004*
PLT (10^9/L)	878	222.07±70.79	220.98±57.14	1.000	0.882
RDWSD (fL)	878	43.52±3.38	42.31±4.15	1.064	0.019*
RDWCV (%)	878	13.51±1.17	13.05±1.47	1.132	0.036*

Table 1 (*continued*)

Table 1 (*continued*)

Variables	n[a]	Poor neurological status (NIHSS score ≥16), n=810	Good neurological status (NIHSS score <16), n=68	OR	P
Fib (g/L)	878	3.44±0.89	2.89±0.74	2.149	<0.001*
PT (s)	878	11.70±1.39	11.17±1.12	1.4	0.001*
INR	878	1.04±0.13	0.98±0.09	83.631	<0.001*
APTT (s)	878	27.88±3.92	27.36±4.13	1.022	0.337
GLU (mmol/L)	878	8.73±4.37	7.75±3.21	1.074	0.022*
ALT (U/L)	878	23.25±12.54	24.57±14.13	0.993	0.457
AST (U/L)	878	26.56±16.16	22.48±10.18	1.024	0.005*
CK (U/L)	878	118.75±123.12	97.93±78.02	1.002	0.054*
CKMB (U/L)	878	18.89±8.57	16.05±8.49	1.025	0.022*
LDH (U/L)	878	295.41±126.92	329.75±186.18	0.999	0.123*
UREA (mmol/L)	878	7.36±4.24	5.71±1.70	1.293	<0.001*
CREA (μmol/L)	878	295.41±126.92	329.75±186.18	1.022	<0.001*
UA (μmol/L)	878	337.29±96.53	320.22±97.30	1.002	0.165*
CHOL (mmol/L)	878	4.35±1.20	4.64±1.00	0.751	0.027*
TG (mmol/L)	878	1.55±1.05	1.74±1.45	0.871	0.288
HDL (mmol/L)	878	1.07±0.34	1.16±0.28	0.309	0.015*
LDL (mmol/L)	878	2.82±1.11	2.90±0.84	0.899	0.470
ApoA1 (g/L)	878	1.14±0.28	1.26±0.24	0.122	<0.001*
ApoB (g/L)	878	0.97±0.28	0.98±0.24	0.836	0.736
Lpa (g/L)	878	23.60±25.37	23.98±32.05	1.000	0.925
FBG (mmol/L)	878	7.79±3.61	7.13±3.05	1.061	0.095*
HbA1C (mmol/mol)	878	6.49±1.02	6.47±1.39	1.007	0.936
HCY (μmol/L)	878	18.48±10.24	19.03±14.36	0.997	0.758
TSH (μU/mL)	878	2.28±3.76	2.07±3.99	1.011	0.668
FT4 (pmol/L)	878	15.09±2.76	15.30±2.40	0.965	0.497
FT3 (pmol/L)	878	4.16±0.81	4.32±0.74	0.745	0.080*

*, variables with P<0.20 were preselected for the multivariable analysis. [a], among the dichotomous variables, n was the number of positive cases. ALT, alanine transaminase; ApoA1, apoprotein A1; ApoB, apoprotein B; APTT, activated partial thromboplastin time; AST, aspartate transaminase; BMI, body mass index; CK, creatinine kinase; CK-MB, creatinine kinase-MB; CREA, creatinine; DNT, door to needle time; Fib, fibrinogen; HGB, hemoglobin; INR, international standardized ratio; LDH, lactate dehydrogenase; Lpa, lipoprotein(a); LDL, low-density lipoprotein cholesterol; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; OTT, onset to thrombolysis; PLT, platelets; PT, prothrombin time; RBD, red blood cells; RDWCV, red cell distribution width – coefficient of variation; RDWSD, red cells distribution width – standard deviation; rt-PA, recombinant tissue plasminogen activator; TG, triglycerides; UA, uric acid; UK, urokinase; WBC, white blood cells.

variable according to its report detected within 48 h of thrombolysis: 0: had no intracranial hemorrhage or massive cerebral infarction; 1: had intracranial hemorrhage or massive cerebral infarction.

The variable of "Brain MRI" was defined as a 2 classification variable according to its report detected within 48 h of thrombolysis: 0: had no intracranial hemorrhage or massive cerebral infarction; 1: had intracranial hemorrhage or massive cerebral infarction.

The variable of "carotid duplex ultrasound" was defined as a 2 classification variable according to its report detected within 48 h of thrombolysis: 0: no carotid atherosclerosis; 1: had carotid atherosclerosis.

The variable of "UCG" was defined as a 2 classification variable according to its report detected within 48 h of thrombolysis: 0: heart was structurally and functionally normal; 1: heart was structurally or functionally abnormal.

The variable of "Lower extremity artery ultrasound" was defined as a 2 classification variable according to its report detected within 48 h of thrombolysis: 0: no arteriosclerosis in the lower limbs; 1: had arteriosclerosis in the lower limbs.

The variable of "Limp deep venous thrombosis, LDVT" was defined as a 2 classification variable according to its report detected within 48 h of thrombolysis: 0: no; 1: yes.

The variable of "ANA" was defined as a 2 classification variable according to its result detected within 48 h of thrombolysis: 0: negative; 1: positive. The variable of "ANCA" was defined as a 2 classification variable according to its result detected within 48 h of thrombolysis: 0: negative; 1: positive.

The variable of "antithrombotic therapy" given within 48h after thrombolysis was defined as a 2 classification variable: 1: only antiplatelet or anticoagulant, 2: both antiplatelet and anticoagulant.

The variable of "rehabilitation" given within 48h after thrombolysis was defined as a multivariate variable: 1: none; 2: acupuncture; 3: kinesitherapy; 4: both acupuncture and kinesitherapy; 5: other therapy, including swallow function rehabilitation.

According to the relevant international standards, the time of admission was determined as the time the patient presented to the emergency stroke center (7).

Bias

Because both stroke centers are advanced stroke centers and have uniform thrombolytic criteria, their examination results are mutually recognized by Grade III, Grade A hospitals. Information bias was avoided.

Study size

The number of cases, according to inclusion and exclusion criteria, at the 2 stroke centers during the study period determined the sample size.

Quantitative variables

The endpoint of the study was defined as the status of the neurological function on 7th day of stroke onset. We used NIHSS score to assess neurological function in the endpoint of the study. When NIHSS score on day 7 after stroke onset was ≥16, the dependent variable Y was denoted as 1. When NIHSS score on day 7 after onset was <16, the dependent variable Y was denoted as 0. We examined the association of the above independent variables with poor neurological function on day 7 after onset.

Statistical methods

Statistical analyses were performed using SPSS version 24.0 (IBM, Armonk, NY, USA). Univariable regression analyses were performed to observe the correlation between each variable and the endpoint. Multivariable regression analysis was performed using binary logistics regression forward stepwise iteration to screen the factors associated with the endpoint. Multivariate regression analysis was also used to deal with confounding factors. The process will be discussed in detail in a later study.

Continuous variables were presented as mean ± standard deviation; categorical variables and ranked variables were presented as n (%). The relationship between variables and the outcome was analyzed by binary logistics regression. Variables with $P<0.20$, which met clinical practice and sample size requirements, were selected for the multivariable regression analysis. The maximum likelihood method was used to select all the variables in the equation with "–2 times" the minimum log likelihood as the factors related to the endpoint. The odds ratio (OR) and 95% confidence interval (95% CI) were calculated.

Our missing data analysis procedures used missing at random assumptions. We independently analyzed 10 copies of the data, each with missing values suitably imputed, in the multivariate logistic regression analyses. We averaged estimates of the variables to give a single mean estimate, and adjusted standard errors according to Rubin's rules.

As the study was retrospective and most patients were hospitalized for more than 7 days in the neurological departments of the 2 hospitals, few patients were lost to follow up. The sensitivity analyses were performed in a future

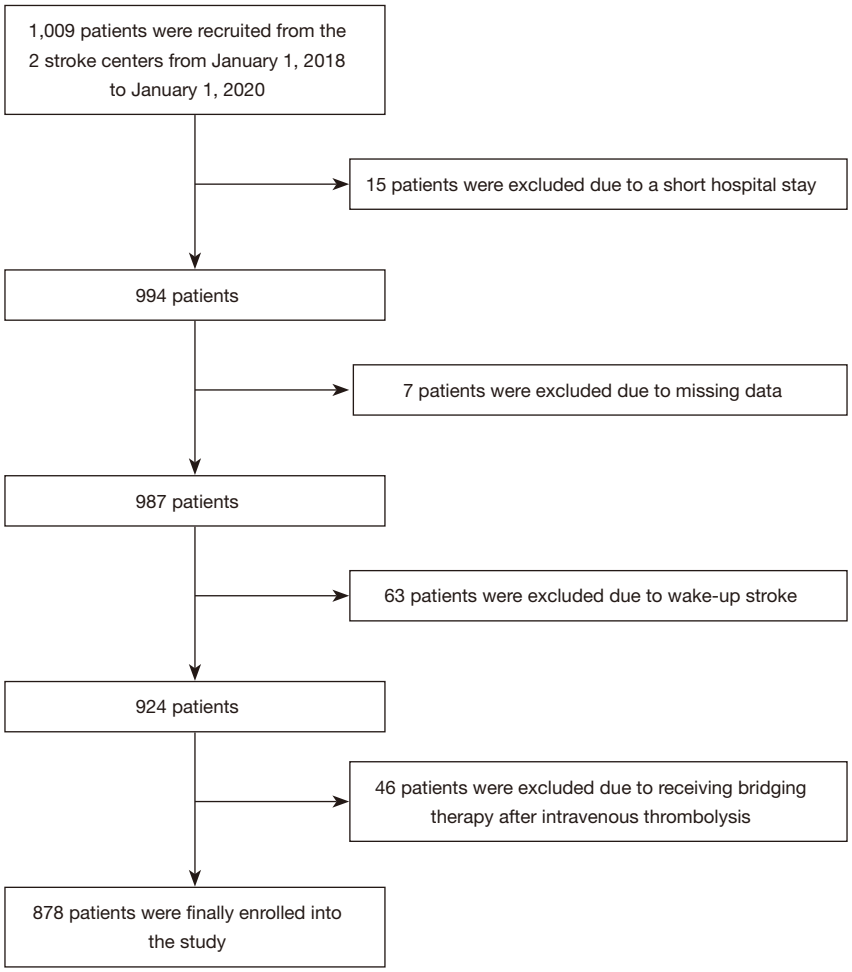

Figure 1 Flow diagram of study selection process.

study on adjusting and controling confounding factors.

Results

Participants

Fifteen patients were excluded because their hospital stays were less than 7 days. Seven patients were excluded due to missing data. Sixty-three patients were excluded due to wake-up stroke. Forty-six patients were excluded because of receiving bridging therapy after intravenous thrombolysis.

A flow diagram was used to show the selection process (*Figure 1*).

Descriptive data

Descriptive statistics and univariable analysis of all variables in the complete set are shown in *Table 1*. The number of participants with missing data for each variable of interest is shown in *Table 2*.

The mean follow-up time in the study was 7.8 days, and the longest follow-up time was 8.5 days.

Data outcome

After univariable analyses, variables with P<0.20, which met clinical practice and sample size requirements, were selected for the multivariable analysis (*Table 1*). We have showed the symptom end points used in survival analysis (see *Table 2*). After multivariable analysis, the following variables were screened as factors associated with the endpoint: age, NIHSS 2, urea nitrogen (UREA), total cholesterol (CHOL), high-density lipoprotein cholesterol (HDL-C), CT2, LDVT, and lipid regulation (*Table 3*).

Table 2 Symptom endpoints used in the survival analysis

Survival rate	Hemiplegia	Lalopathy	Sensory disturbance
Symptom resolved	648 (80%)	482 (60%)	614 (77%)
Censored	81 (10%)	64 (8%)	72 (9%)
Never symptomatic	0	121 (15%)	24 (3%)
Data missing	81 (10%)	137 (17%)	88 (11%)
Total	810 (100%)	804 (100%)	798 (100%)

Table 3 Multivariable logistic regression analysis of factors related to poor neurological function

Variables	β	P	OR	95% CI	
				Lower	Upper
Age	0.095	<0.001	1.099	1.052	1.149
NIHSS 2	0.289	<0.001	1.286	1.201	1.377
CHOL	0.478	0.034	1.614	1.036	2.514
HDL-C	–3.268	0.000	0.038	0.007	0.202
UREA	0.187	0.010	1.205	1.045	1.390
Lipid regulation	–2.736	0.000	0.065	0.020	0.215
CT2	1.817	0.000	6.153	2.696	14.045
LDVT	1.481	0.005	4.398	1.560	12.398

CI, confidence interval; CHOL, total cholesterol; CT2, computed tomography 24 h after thrombolysis; HDL-C, high-density lipoprotein cholesterol; LDVT, lower limb deep venous thrombosis; NIHSS 2, National Institutes of Health Stroke Scale assessed immediately after thrombolysis; OR, odds ratio; UREA, urea nitrogen.

By comparing ORs and 95% CIs, variables of age (OR: 1.099, 95% CI: 1.052–1.194, P<0.001), NIHSS 2 (OR: 1.286, 95% CI: 1.201–1.377, P<0.001), CHOL (OR: 1.614, 95% CI: 1.036–2.514, P<0.05), UREA (OR: 1.205, 95% CI: 1.045–1.390, P<0.05), CT2 (OR: 6.153, 95% CI: 2.696–14.045, P<0.001), and LDVT (OR: 4.398, 95% CI: 1.560–12.398, P<0.01) were found to be associated with poor neurological function on day 7 after stroke onset. The variables lipid regulation (OR: 0.065, 95% CI: 0.02–0.215, P<0.001) and HDL-C (OR: 0.038, 95% CI: 0.007–0.202, P<0.001) were found to be protective factors for poor neurological function.

Continuous variable data participated in the statistics with prototype. The dependent variable was a dichotomous variable, which was defined by the NIHSS score on day 7 after onset.

The findings of the present study indicated that, for every 1-year increase in age, the risk of poor neurological function in hospital increased by 9.9% for AIS patients who underwent intravenous thrombolysis. For every point increase in the NIHSS score evaluated immediately after thrombolytic therapy, the risk of in-hospital poor neurological function after intravenous thrombolysis increased by 28.6%. For every 1 mmol/L increase in CHOL, the risk of poor neurological function after intravenous thrombolysis increased by 61.4%. For every 1 mmol/L increase in HDL-C, the risk of poor neurological function after intravenous thrombolysis reduced by 96.2%. The risk of poor neurological function for patients with lipid-regulating therapy 48 h within intravenous thrombolysis was 0.065 times as much as those without lipid-regulating therapy. The risk of poor neurological function for patients with abnormal report of brain CT scanned 24 h after intravenous thrombolysis was 6.153 times as much as those with normal report. The risk of poor neurological functional in patients with LDVT revealed in the lower extremity venous color Doppler ultrasound after intravenous thrombolysis was 4.398 times as much as that of patients without LDVT. For every 1 mmol/L increase in UREA, the risk of poor neurological function

Table 4 The blood pressure level and the deterioration of the nervous system among different subtypes of ischemic stroke

Subtypes of ischemic stroke	n	Systolic pressure	Diastolic pressure	NIHSS 1
LAA	482	150.98±21.45	85.70±13.07	9.32±6.01
CE	81	154.05±27.05	88.42±18.12	11.88±7.41
SAA	290	147.62±20.20	85.86±13.49	3.41±2.64
SOE	14	150.14±15.10	90.71±22.18	6.86±3.26
SUE	11	155.09±24.72	95.27±15.86	4.18±3.89

Subtypes of ischemic stroke: the ischemic stroke was divided into 5 subtypes according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification. LAA, large artery atherosclerosis; CE, cardioembolism; SAA, small artery atherosclerosis; SOE, stroke of other determined etiology; SUE, stroke of undetermined etiology; NIHSS 1, the National Institutes of Health Stroke Scale (NIHSS) scored before intravenous thrombolysis.

Table 5 The distribution characteristics of risk factors among high-risk stroke populations of different ages and genders

Risk factors	Age		Sex	
	≤62 years old	>62 years old	Male	Female
NIHSS 2	6.07±0.30	7.03±0.33	6.71±0.27	6.18±0.39
CHOL	4.65±0.98	4.58±1.05	4.47±0.95	4.93±1.09
UREA	5.48±1.75	6.19±2.27	5.89±1.91	5.71±2.35
CT2				
0	87.5%	78.1%	81.5%	85.7%
1	12.5%	21.9%	18.5%	14.3%
LDVT				
0	95.9%	90.2%	94.0%	90.8%
1	4.1%	9.8%	6.0%	9.2%

CT2, brain computed tomography examined 24 h after thrombolysis (0, had no intracranial hemorrhage or massive cerebral infarction; 1, had intracranial hemorrhage or massive cerebral infarction). LDVT, lower limb deep venous thrombosis (0, no; 1, yes). NIHSS2, NIHSS score immediately after thrombolysis; UREA, urea nitrogen; CHOL, total cholesterol.

after intravenous thrombolysis increased by 20.5%. We also showed the blood pressure level and the deterioration of the nervous system among different subtypes of ischemic stroke (see *Table 4*) and showed the distribution characteristics of risk factors among high-risk stroke populations of different ages and genders (see *Table 5*).

The interaction, adjusting, and control confounding factors will be explained in a later study.

Discussion

Key results

AIS is as result of a thrombus or embolus block in the cerebral arteries and accounts for a large proportion of all stroke patients (4,5). At the early stage of acute cerebral infarction, intravenous thrombolysis is a safe and reliable option, but it is not entirely without risk (7,9-11). Identifying the risk factors for poor neurological function in AIS patients after intravenous thrombolysis in order to adjust clinical strategies is crucial for clinical patient management. The present study was based on the overall data of AIS patients from 2 advanced stroke centers following intravenous thrombolysis. The thrombolytics drugs included rt-PA and domestic UK. Univariable and multivariable analyses were performed to screen the variables related to the endpoint. By comparing the ORs and their 95% CIs, risk factors and protectors were

identified. The results suggested that old age, high levels of CHOL and UREA, high NIHSS scored immediately after thrombolysis (NIHSS2), bad result of brain CT 24 h after thrombolysis, and LDVT could predict poor neurological function after thrombolysis for AIS. Lipid-regulating therapy and high level of HDL-C could reduce the risk of poor neurological function.

Limitations

The present study has some limitations. First, the follow-up time was short. Future studies should extend the follow-up time to 3 or 6 months after the onset of AIS. Second, it may be more meaningful to perform a multi-center study and comparative analysis with other regions.

Interpretation

Increasing age has an important impact on the incidence, mortality, and long-term outcome of AIS (27). In their study, Rejnö *et al.* suggested that age could predict the deterioration of neurological function after stroke (28). Advanced age could lead to the dysfunction of neurovascular units and neurodegenerative changes in stroke patients (29). In the present study, age was a risk factor for poor neurological function after intravenous thrombolysis (OR: 1.099, 95% CI: 1.052–1.194, P<0.001), and its clinical significance was that for every 1-year increase in age, the risk of poor neurological function in hospital increased by 9.9% for AIS patients who underwent intravenous thrombolysis. Therefore, the relationship between age and the endpoint in the present study was consistent with the previous published studies we have cited above.

Stroke severity can be determined according to the degree of neurological impairment (e.g., impairment of consciousness, language, behavior, visual field impairment, and motor impairment). NIHSS score is also increasingly used in clinical practice to assess changes in neurological function after intravenous thrombolysis and determine its therapeutic effect (30). In the present study, NIHSS2 was found to be a risk factor for poor neurological function after intravenous thrombolysis (OR: 1.286, 95% CI: 1.201–1.377, P<0.001), and the clinical significance was that, for every point increase in the NIHSS score evaluated immediately after thrombolytic therapy, the risk of in-hospital poor neurological function after intravenous thrombolysis increased by 28.6%. Therefore, the relationship between the variables of NIHSS2 and the endpoint in the present study was consistent with the previous published studies we have cited above.

The correlation between blood lipids and stroke outcome varies depending on the components of blood lipids. CHOL is an adjustable risk factor, and some scholars believe that CHOL level is closely associated with the onset of first ischemic stroke (31). Globally, high cholesterol levels (>185 mg/dL) were associated with a 24% increase in stroke-related disability-adjusted life years from 1990 to 2013 (32). Most studies have found that CHOL levels are positively correlated with the risk of ischemic stroke. In the present study, CHOL was a risk factor for the endpoint (OR: 1.614, 95% CI: 1.036–2.514, P<0.05). Its clinical significance was that, for every 1 mmol/L increase in CHOL, the risk of poor neurological function after intravenous thrombolysis increased by 61.4%. The correlation between CHOL and the endpoint in the present study was consistent with the previous published studies we have cited above.

HDL-C is a strong and independent negative predictor of cardiovascular and cerebrovascular diseases. The beneficial effect of HDL-C is largely due to its key role in the reverse transport of cholesterol, namely the transport of excess cholesterol from peripheral tissues to the liver. There is increasing evidence that HDL-C also has anti-inflammatory, antioxidant, and vasodilator characteristics, reducing atherosclerosis (33). Gu *et al.* analyzed 6 cohort studies involving 267,500 Chinese patients and showed that low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) levels were positively correlated with ischemic stroke, while HDL-C levels showed a negative correlation (34). In their study, Li *et al.* suggested that the ATP-binding cassette transporter A1/apolipoprotein E/HDL-C signaling pathway might be involved in the myelination and oligodendrocyte cytogenesis of ischemic brain tissues after stroke, which could repair the white matter damage of the central nervous system caused by stroke and promote the white matter remodeling of ischemic brain tissues, thereby facilitating the recovery of neurological function in the late stage of ischemic stroke (35). Therefore, HDL-C is associated with the functional outcome of ischemic stroke and might be a protective factor for the bad outcome. In the present study, HDL-C was a protective factor for poor neurological function after intravenous thrombolysis, which was consistent with the previous published studies we have cited above. After multivariable analysis, the OR of HDL-C was 0.038 and 95% CI was 0.007–0.202. The clinical significance was that, for every 1 mmol/L increase

in HDL-C, the risk of poor neurological function after intravenous thrombolysis reduced by 96.2%.

As a result, lipid-regulating therapy is important. In the present study, we also found that the variable of lipid regulation was the protective factor to the endpoint (OR: 0.065, 95% CI: 0.02–0.215, P<0.001). Its clinical significance was that the risk of poor neurological function for patients with lipid-regulating therapy 48 h within intravenous thrombolysis was 0.065 times as much as those without lipid-regulating therapy. Intravenous thrombolysis and endovascular thrombectomy can quickly achieve reperfusion to reduce disability (7,9-11,36). However, intravenous thrombolysis has an increased risk of symptomatic intracerebral hemorrhage (37). Non-contrast CT can exclude intracranial hemorrhage, and it is crucial to recheck the head CT as soon as possible after thrombolysis (after 24 h, and before the administration of antiplatelet drugs) (7). In the present study, CT2 was a risk factor for the endpoint (OR: 6.153, 95% CI: 2.696–14.045, P<0.001). Its clinical significance was that the risk of poor neurological function for patients with an abnormal report of brain CT scanned 24 h after intravenous thrombolysis was 6.153 times as much as those with a normal report, which was consistent with the previous published studies we have cited above.

LDVT or lower extremity venous thrombosis is a severe comorbidity of ischemic stroke. Paralysis after stroke is a common cause of lower extremity venous thrombosis. Pan *et al.* analyzed clinical characteristics and accessible biochemical parameters to develop and validate a nomogram for predicting the risk of deep vein thrombosis in patients with acute stroke within 14 days (38). Liu *et al.* conducted a study on 679 stroke patients (including 507 with ischemic stroke and 172 with hemorrhagic stroke) and found that 21.1% of patients with ischemic stroke (n=107) were affected by deep vein thrombosis (39). Intermuscular veins, especially fibular veins, were the most susceptible. Ha *et al.* studied Asian AIS patients with lower extremity deep venous thrombosis, and found that females and higher NIHSS scores were independently associated with lower extremity deep venous thrombosis (40). Compared with D-dimer screening, lower extremity deep venous color Doppler ultrasound of patients with severe neurological deficits might be more conducive to diagnosing deep vein thrombosis in Asian AIS patients. Decreased activities of the lower extremities or joint contractures caused by stroke and other reasons could be the main contributors to deep vein thrombosis of the lower extremities, which can further lead to a prolonged rehabilitation process (41). After completing the acute phase of treatment, most stroke patients need rehabilitation. It usually takes months or even years for patients to have full restoration of their extremity function. Paralyzed limbs might be restricted in daily activities, such as turning over, getting up, and moving short distances, due to decreased activities. After lower extremity venous thrombosis, the rehabilitation exercise of the paralyzed limbs will further decrease, which will lead to a longer recovery time of the extremity function, and severe neurological deficits and poor outcome. Therefore, LDVT could be a risk factor for poor neurological function after stroke. In the present study, we found that LDVT was a risk factor for the endpoint (OR: 4.398, 95% CI: 1.560–12.398, P<0.05), and its clinical significance was that the risk of poor neurological function in patients with LDVT revealed in the lower extremity venous color Doppler ultrasound after intravenous thrombolysis was 4.398 times as much as that of patients without LDVT.

Peng *et al.* found that both high and low levels of blood urea nitrogen (BUN) were associated with high risk of ischemic stroke (42). Deng et al found that elevated BUN/creatinine (Cr) is associated with poor 3-month outcome in AIS patients with high HDL-C levels (43). In the present study, UREA (or BUN) was found to be a risk factor for poor neurological function after intravenous thrombolysis. The OR value was 1.205 and 95% CI was 1.045–1.390 (P<0.05). The clinical significance was that, for every 1 mmol/L increase in UREA, the risk of poor neurological function after intravenous thrombolysis increased by 20.5%. Our next research plan is to make use of these risk factors to establish a prediction model and provide individualized prediction and intervention for patients.

Regarding the strategies of screening variables into the multivariable regression, the baseline variables considered clinically relevant, and had a univariable relationship with the outcome, were included in the multivariable risk regression model (44). The variables were carefully selected. It must ensure the conciseness of the final model at first. As candidate variables that might impact the outcome event, from the perspective of clinical specialty, its role must first be acceptable to people, and should be reasonably explained from a certain physiological mechanism or pathway. The baseline variables of the present study included demographic data [e.g., sex, age, and BMI, lifestyle (e.g., smoking and alcohol consumption)], medical history (e.g., hypertension, diabetes, coronary heart disease, arrhythmia, hyperlipidemia, and past stroke), examinations (blood test indicators and other examination items), treatments (thrombolytics

type, DNT, and OTT time), and exposure/treatment factors (NIHSS score after thrombolysis, subsequent related antiplatelet, anticoagulation, lipid regulation, and rehabilitation). From the above variables, and by referring to the previously published literature, the variables screened by univariable regression analysis with P>0.2 and conformed to clinical practice, were summarized and used as key candidate variables for multifactor regression analysis.

Second, the variables were screened from the results of the univariable analysis. The relationship between traditional univariable analysis and univariable regression analysis was essentially equivalent. In the univariable analysis, differences in single factors among groups were analyzed by *t*-test, χ^2-test, and analysis of variance. Through these univariable analysis methods, distribution differences of the means or percentages between 2 or among multiple groups can be simply and directly observed. Univariable regression analysis included only 1 factor in the regression model for fitting when constructing the regression model. Therefore, the univariable regression analysis was equivalent to the traditional univariable analysis methods used in the present study. The *t*-test was equivalent to simple linear regression, while analysis of variance was equivalent to multiple linear regression. Similarly, the results of the analysis of variance and the univariable linear regression were equal in value to a certain extent, but they might not have exactly the same P value. In the present study, the baseline variables were analyzed by univariable regression analysis individual, and the P value is shown in *Table 1*.

Statistical significance in the univariable analyses was set at P<0.05, and the inclusion criteria were appropriately extended to P<0.20 in the present study (45), effectively avoiding the omission of some important variables, as their real effects might be underestimated or neglected due to the limitation of the P value.

When performing the multivariable regression analysis, categorical variables with 3 or more variables need to set dummy variables because parametric regression is made in the framework of a generalized linear model, and the latter has a linear trend. If dummy variables were not set, the categorical variables with 3 or more categories were selected into the multivariable adjustment, and the relationship between different categories of the variable had equivalent effects on the outcome during the statistical analysis. However, many medical variables were multicategorical variables, and there was no such equidistant relationship. To better explain which variable had a greater impact on the outcome, a reference must be set, namely the dummy variable.

Generalizability

The data of the present study were from the 2 provincial advanced stroke centers. The facilities, management, and skill level of the medical staff at the 2 centers were configured to a uniform standard. The examination reports could be mutually recognized. Data collection and statistical analysis were done by the same person. In the study, the variables of Age, NIHSS2, CHOL, UREA, CT2, and LDVT were found to be risk factors of poor neurological function after thrombolysis for AIS. Lipid regulation and HDL-C were found to be protective factors of poor neurological function. As a result, the conclusion of the study has credibility and generalizability.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3652/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3652/dss

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3652/coif). The authors have no conflicts of interest to declare.

Ethical statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Baoding No. 1 Central Hospital (No. 2021[012]) and had been put on record in the Second Hospital of Hebei Medical University. Individual consent for this retrospective analysis was waived.

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